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THE AGING COCHLEAR HAIR CELL

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Abstract

Specimens from the organ of Corti were taken from regions which appeared normal in the cytocochleogram as evaluated with the Nomarski optics. Ultrastructural, qualitative analyses of aging cochlear hair cells in the guinea pig showed, however, principally five distinct types of pathological changes: (1) disintegration of the cuticle; (2) increased amounts of intracellular lamellar structures and submembrane cisternae; (3) aggregations of electron optically dense particles; (4) lysosome-like structures; and (5) vesiculation of cytoplasm. Stereocilia remained intact also in cells where the cuticular plate showed severe degeneration. Outer hair cells showed more extensive cytological changes than inner hair cells. The ultrastructural pathology in aging cochlear hair cells is specific and is a sign of dysdifferentiation of their specific morphology although the hair cells survive for a long time in a more or less dysdifferentiated state. Hair cell changes were primary, leaving afferent and efferent nerve terminals initially morphologically intact.

Key words: Hearing, aging, cochlea, hair cell, morphology, pathology

Introduction

The auditory system, like all other systems in the body, changes with aging. Age related loss of auditory function, recorded by behavioral and electrophysiological techniques, have been analyzed in detail in a number of laboratory animals as, e.g., the mouse, the Mongolian gerbil and the guinea pig (13, 16, 23). Using auditory brainstem recordings Dum and von Wedel (17) showed that in aging guinea pigs a loss of sensitivity occurred, the amplitudes of all potentials showed a uniform reduction with advancing age whereas the latencies remained unchanged.

Age related morphological degeneration of sensory receptors, i.e., the hair cells, occurs both in the human and in a number of animal species (6-8, 24, 25, 30, 31, 38, 40). Hair cell loss in aging occurs in the entire cochlea but predominantly in the base and at the apex (7, 30). Degeneration of hair cells in the base of the cochlea is reflected functionally by high tone sensorineural hearing loss and is the most easily explainable. So far, there is no definite explanation for the progressive apical hair cell loss. An atrophy of the stria vascularis occurs with advancing age at the apical part of the cochlea and might contribute to a disturbance of inner ear fluid homeostasis and thereby indirectly cause hair cell degeneration.

So far morphological studies on the aging cochlea have been focused mainly on present and missing hair cells, in general using the cytocochleogram technique (6, 7, 15, 18, 30, 31, 48). The outer hair cells appear more vulnerable than the inner hair cells (7, 20, 47). A greater (maximal) hair cell loss occurs in the third row of outer hair cells and to a smaller degree in the second and first rows (14).

This study presents an ultrastructural qualitative analysis of aging cochlear hair cells which, in the light microscope, using the cytocochleogram technique showed normal morphology.

Materials and Methods

The material was comprised of 17 pigmented guinea pigs with an age between 4 and 6 years. Only a few of the animals were obtained from breeders whereas the majority of the guinea pigs were donated from private owners. According to available information, the animals had neither been treated with ototoxic antibiotics nor exposed to severe acoustic trauma.

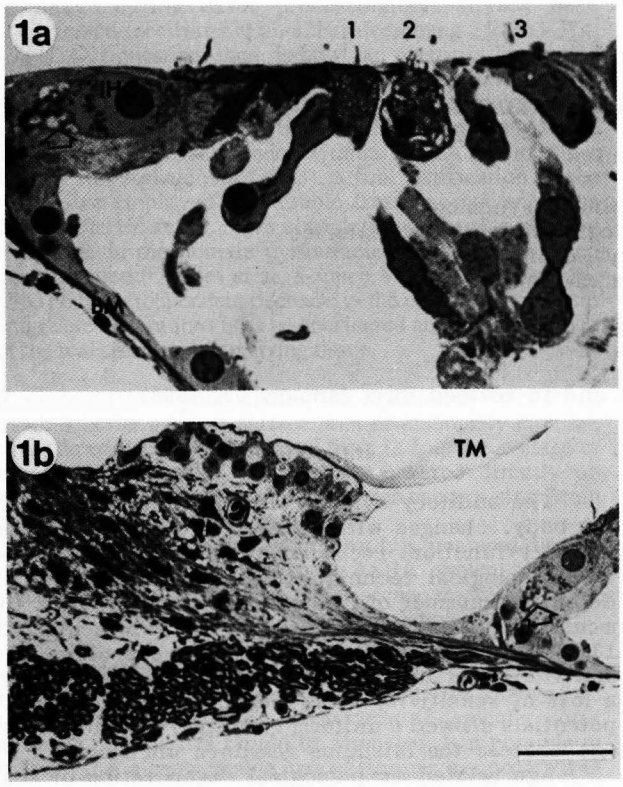

Fig. 1. Light micrograph (LM). Section through the basal coil of a 4-year-old cochlea. (A) Vesiculation is present in all three rows of outer hair cells (1-3) but stereocilia are still identified at their surfaces. Below the inner hair cell (IHC) "empty" regions (unfilled arrow) occur. (BM), basilar membrane. Oil immersion. (B) Same specimen as in (A). Numerous myelinated cochlear nerve fibres (N) remain. Cells in the spiral limbus have normal morphology. (TM), tectorial membrane. Bar = 50 μm.

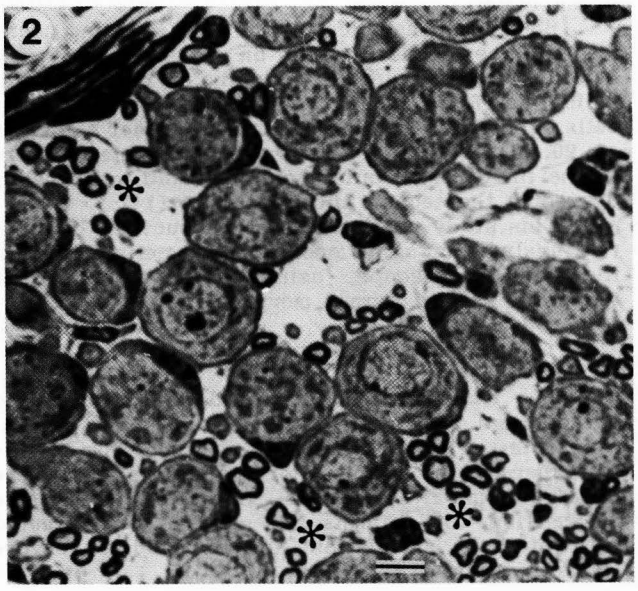

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Fig. 3. Electron micrograph (EM). Outer hair cell from first row (OHC I) from basal coil of a 5-year-old cochlea. Lysosome-like structures are indicated with an unfilled arrow. The cuticular plate (C) has the form of a cone directed into the supranuclear cytoplasm. Although stereocilia (S) are present, they lack rootlets into the cuticle. The cuticular plate fills only a part of the sensory cell surface (confirmed at serial sectioning) leaving other parts (asterisks) free from cuticular support. Bar = 1 μm.

Fig. 4. EM. Outer hair cell in second row (OHC II) from basal coil of a 5-year-old cochlea. Normal ultrastructure of OHC II, Deiter's cells (DC), afferent (A) and efferent (E) nerve endings. In one region, a possible afferent nerve shows a concentric whorl (arrow), indicating early degeneration. Bar = 2 μm.

Fig. 5. EM. Outer hair cell in second row from upper basal coil of a 5-year-old cochlea. Upper part of hair cell. Cuticular-like material extends from the cuticle (C) into the interior of the hair cell (asterisks) and along the cell membrane (unfilled arrow). Rootlets can no longer be identified in the cuticle. (L), lysosome-like inclusion bodies. Several mitochondria appear ultrastructurally normal. Bar = 1μm.

Fig. 6. EM. Outer hair cell in first row from a 6-year-old cochlea. Basal coil. Stereocilia (S) are still present and appear ultrastructurally normal, whereas the cuticular plate (asterisk) is disintegrating. Sensory hair rootlets are present (unfilled arrow). Lysosome-like material (L) can be found also within the cuticular plate. The hair cell cytoplasm seems empty, which has been interpreted as a sign of its degeneration. Along the hair cell membrane a striated structure is present, possibly reflecting connections between the cell membrane and the subsurface cisternae. Bar = 1 μm.

After decapitation of the guinea pigs, the temporal bones were removed, the bulla tympanica was opened and the inner ear was fixed with 3% glutaraldehyde in 0.1% M phosphate buffer by perfusion through the oval and round windows and through an opening made at the apex of the cochlea. The specimens were postfixed in 1% osmium tetroxide and were, after rinsing in buffer, dehydrated in increasing concentrations of alcohol and embedded in Epon mixture. The cochleae were prepared according to the cytocochleogram technique visualizing all areas

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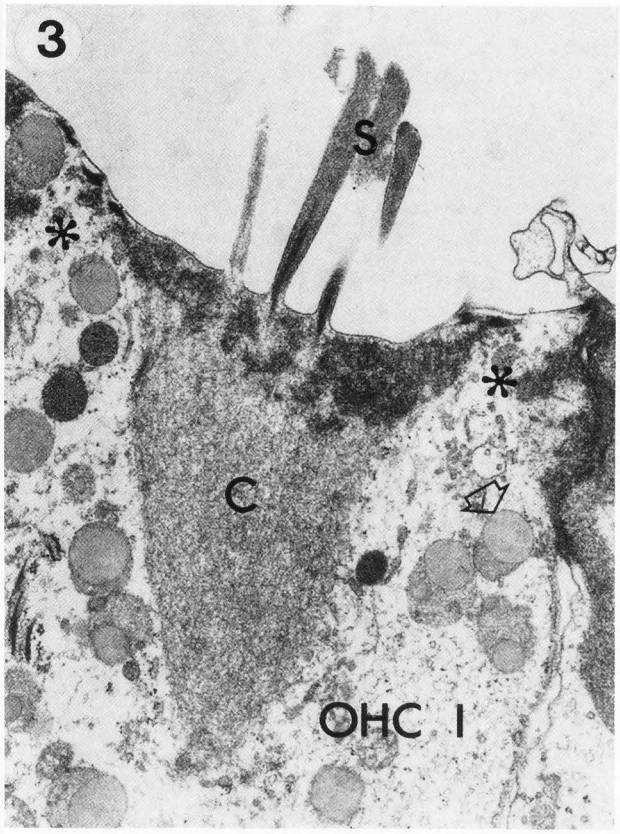
Fig. 2. (at left) LM. Spiral ganglion from basal coil of a 4-year-old cochlea at a level where outer and inner hair cells are present. The ganglion cells show a normal morphology. There are few myelinated nerve fibers. Areas lacking myelinated nerve fibers are indicated with asterisks. Oil immersion. Bar = 10 μm.


3
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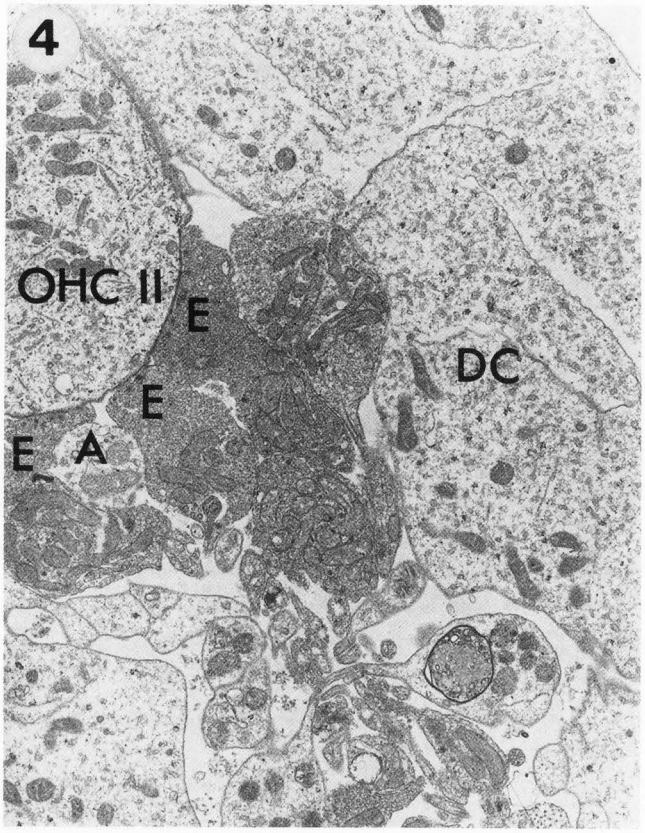
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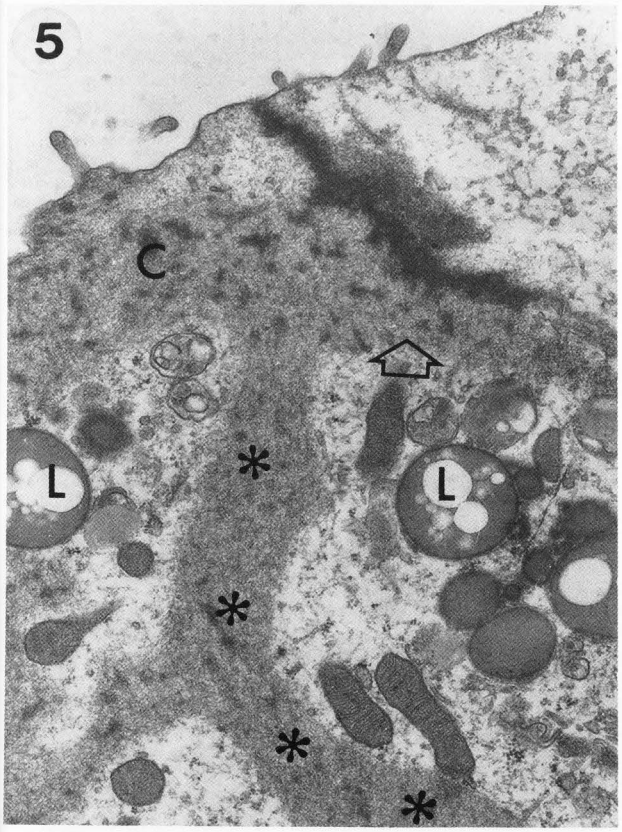
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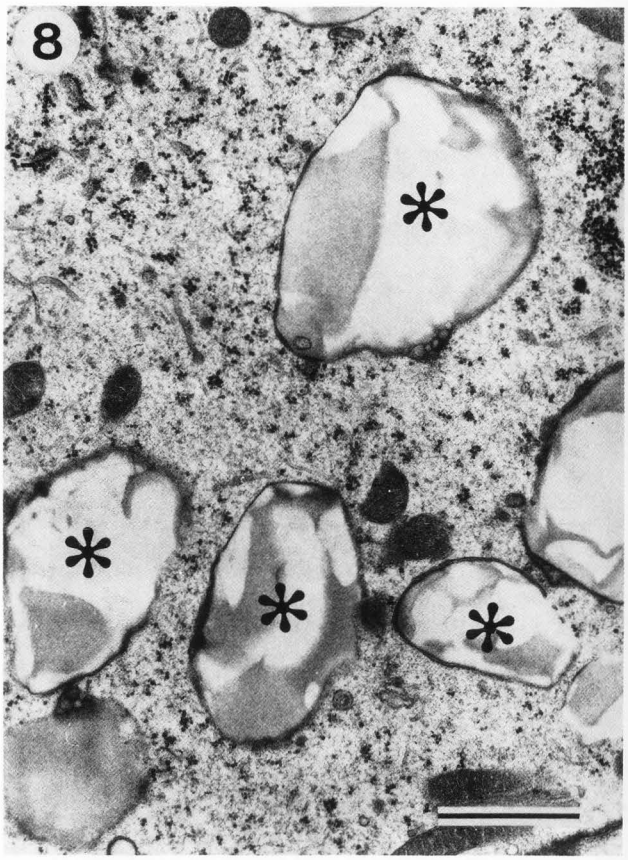
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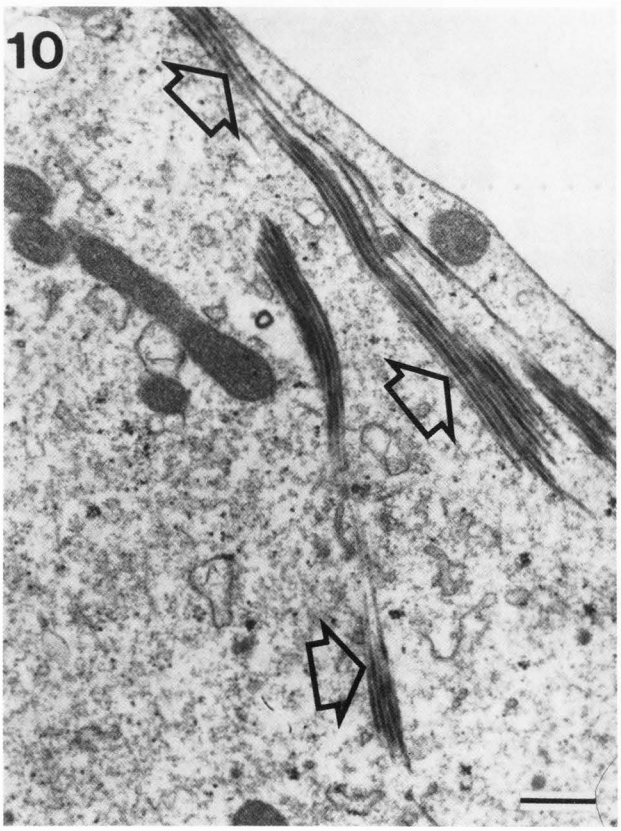
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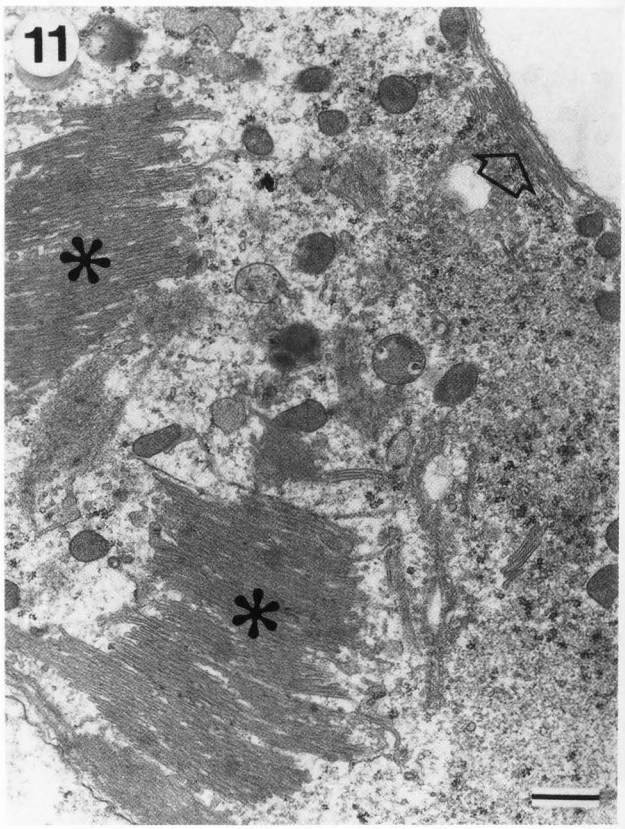
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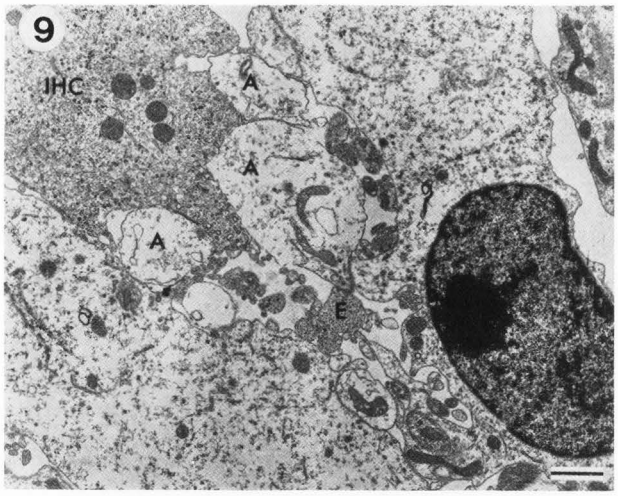
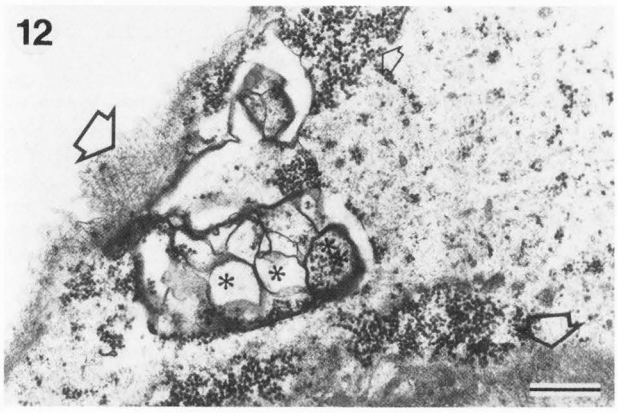




Legends for Figs. 7, 8, 10 and 11 (on left).

Fig. 7. EM. Outer hair cell in first row from second coil of a 5-year-old cochlea. Stereocilia (S) are present and their rootlets penetrate into the cuticular plate (C). Lysosome-like (L) inclusion bodies occur in the cuticle. The border of the cuticle adjacent to the hair cell interior is indistinct and cuticula-like material (asterisks) is found in the supranuclear cytoplasm. Bar = 1 μm.

Fig. 8. EM. Outer hair cell in first row from basal coil of a 6-year-old cochlea. Although cell organelles appear ultrastructurally normal, large membrane-bound inclusion bodies (asterisks) occur intracellularly. Bar = 1 μm.

Fig. 10. EM. Outer hair cell in first row from second coil of a 5-year-old cochlea. The hair cell contains accumulations of membrane-like material (unfilled arrows) quite near to the cell membrane but also extending into the cytoplasm. Bar = 1 μm.

Fig. 11. EM. Outer hair cell in second row from basal coil of a 4-year-old cochlea. Accumulations of lamellar structures (asterisks) in otherwise normal cytoplasm. Similar material is observed also adjacent to the cell membrane (unfilled arrow). Bar = 1 μm.

Fig. 9 (on left). EM. Inner hair cell (IHC) from second coil of a 4-year-old cochlea. The ultrastructure of the hair cell is normal, whereas afferent (A) nerve endings below the IHC are considerably swollen. Efferent nerve (E) terminals appear normal. Bar = 2 μm.

Fig. 12. EM. Outer hair cell in first row from basal coil of a 5-year-old cochlea. Along the cell membrane, focal regions occur with fibrillar-like substructure (large unfilled arrows). In the otherwise normal cytoplasm, accumulations of electron-dense bodies (larger than ribosomes) occur (small unfilled arrow), sometimes surrounded by a membrane (double asterisks). A few membrane-bound vesicles appeared empty (after releasing the electron-dense particles?). Bar = 0.5 μm.

form the basal hook to the apex. Blocks were taken for radial and perpendicular sectioning of the organ of Corti from areas that showed normal conditions when surface preparations were viewed under Nomarski optics. The prerequisite to section these blocks was that the myelinated nerve fibers also showed a normal morphology.

Light microscopic sections were stained with toluidine blue and analysed in a Zeiss Axiophot microscope. Ultrathin sections were stained with uranyl acetate and lead citrate and analysed in a JEOL 1200 EX transmission electron microscope. The results presented below are based on 184 ultrastructural specimens from different regions.

Results

In spite of the fact that the organ of Corti showed normal morphology in the Nomarski optics, histological sections sometimes showed varying degrees of pathology, mainly vesiculation of cytoplasm, preferentially in the outer hair cells (Fig. 1). In these cases, also small areas of clearing occurred below the inner hair cell but the myelinated nerve fibers showed a normal morphology. Sections through the spiral ganglion showed normal morphology but a reduced number of myelinated nerve fibers was suspected (Fig. 2).

In the cochlear hair cells the ultrastructural pathological changes could be grouped into five main types: alterations of the cuticle, intracellular lysosome-like structures, increased amounts of membrane/submembrane cisternae and intracellular lamellae, aggregations of electron optically dense particles (sometimes surrounded by a membrane) and vesiculation of cytoplasm.

The cuticular plate could show non-distinct delineation towards the interior of the hair cell but also form cones extending into the supranuclear part, could form strands growing intracellularly, not only into the supranuclear cytoplasm but also along the cell membrane, or disintegrate leaving only focal areas of cuticular-like material (Figs 3, 5-7). In all these cases normal stereocilia were still present although the sensory hair rootlets could be poor or sometimes even lacking. In all cells with pathological changes of the cuticle, cytological changes with lysosome-like structures were identified (Figs 3, 5-8). Mitochondria appeared, however, rather normal.

The nerve terminals below outer hair cells were normal. Only occasionally minor alterations were

found in afferent nerve endings (Fig. 4). Below the inner hair cells many afferent nerve endings were swollen (Fig. 9) but the efferent nerve endings appeared ultrastructurally normal.

Accumulations of membrane-like material close to the outer cell membrane or extensive accumulation of a lamellar structure occurred in cells with otherwise a normal ultrastructure except for the lysosome-like inclusion bodies (Figs. 10-12). Increased amounts of submembranous cisternae, sometimes split by aggregations of electron optically dense particles, were frequent (Fig. 13).

Cells with an unspecific vesiculation of the hair cells showed in surprisingly many cases cuticular plates and remaining stereocilia (Figs. 14-16). Specific mitochondrial changes did not occur.

Discussion

The clinical concept of senescence of hearing in humans is well established (25, 34). Aging occurs in all mammalian systems (28, 29). In many highly specialized systems aging seems to be the result of cells simply drifting away from their proper state of differentiation (9). Aging appears like an ontogeny in reverse and almost as well ordered. In such a model concept, aging is thought to begin in higher-order states of differentiation and working backwards. The more complicated or complex the function, the earlier it starts to decline during aging (36).

A natural drifting away of cells to a less effective state of differentiation has been named dysdifferentiation. The bases for this is that the proper differentiated state of cells is naturally unstable and requires positive efforts for its maintenance. The hair cells of the inner ear are highly specialized. Age dependent changes in gene expression and subsequent dysdifferentiation state of cells has been shown in a number of organ systems, e.g., liver and brain tissues (33) and is therefore likely to occur also in hair cells. Major evidence for dysdifferentiation of highly specialized structures during aging has been summarized by Cutler (10, 11). It was shown that there is no evidence that aging is a result of an accumulation of damage leading to an impairment of general cell function.

The correlation of clinical and histological findings in auditory impairment is often poor (25). This is probably the result of the techniques so far used: correlations are often made between audiograms and hair cell counts without taking into consideration the ultrastructural quality of the remaining hair cells. In experimental animals, it is possible to make refined frequency-specific electrophysiological measurements but these do not always correlate with the integrated response of sound stimulation of the cochlea (18). The present study showed that considerable ultrastructural changes appeared in remaining hair cells of the aging guinea pig cochlea. The most striking and common ultrastructural feature was the degeneration of the cuticular plate. An intact cuticle is of utmost importance for anchoring the sensory hairs which register sound induced fluid motion and are the keys for proper hair cell stimulation (26, 45). The stereocilia are extremely stiff and are composed of actin filaments which are anchored to the cuticular plate in a complex way (21, 42). Changes in the structure of the cuticle must cause changes in the detection of stimuli from stereocilia.

Fig. 13. EM. Outer hair cell in first row from second coil of a 5-year-old cochlea. Excess amounts of submembrane cisternae, (filled arrow). Interspersed among the cisternae accumulations of electron-dense particles occur as well as in the otherwise normal cytoplasm (unfilled arrow). Some of these particles (asterisk) are enclosed by a membrane. Bar = 1 μm.

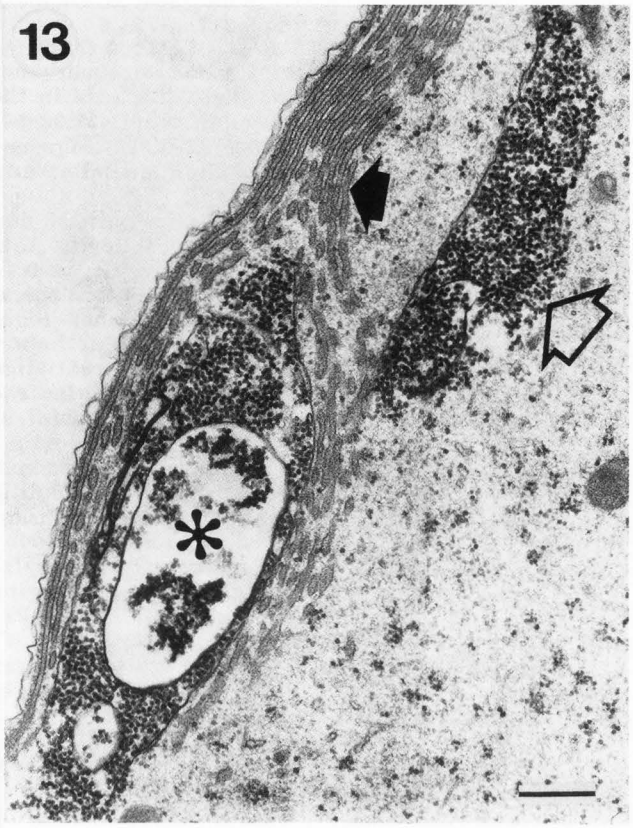
Figs. 14-15. EM. Outer hair cell in third row (OHC III) from second coil of a 4-year-old cochlea. Focal regions with edema of cytoplasm but most mitochondria appear ultrastructurally normal. Bar = 1μm.

Fig. 16. EM. Outer hair cell in second row (OHC II) from second coil of a 4-year-old cochlea. Considerable vesiculation of cytoplasm. The cuticle (C) is ultrastructurally normal. Most mitochondria (filled arrows) are normal. Many lysosome-like (L) inclusion bodies occur in the cytoplasm as well as accumulations of cuticula-like material (asterisks). Bar = 1 μm.

Since also the cuticle is largely composed of actin, it seems that the formation of actin is a weak point in the hair cell metabolism and can be affected not only early in genetic inner ear disorders (43) but also with increasing age. Similar findings have been documented in the aging vestibular hair cell (2). Changes in actin composition with increasing age have been reported in several mammalian cell types. In cell cultures, the ability to assemble and reassemble actin-actin and actin-membrane associations is reduced with age (32). Hence, a relative slowness occurs in cell spreading/movements.

The age related hair cell loss is larger among the outer hair cells than among the inner hair cells (6, 15, 30, 31, 48). Ultrastructural pathological changes in the present study occurred predominantly in outer hair cells leaving most inner hair cells rather intact. Thus, also in age related cochlear hair cell pathology a differential vulnerability between the two types of hair cells was present, as also described for ototoxic drugs, noise and metabolic disorders (4, 14). A difference in function between outer hair cells and inner hair cells is well established (12). Differences in function are in part also reflected by differences in the cytoskeletal composition of inner and outer hair cells (3, 5, 44). Outer hair cells may respond to a number of stimuli by contraction of the hair cells (22). This contraction is mediated by interactions between contractile (actin) fibers and the submembranous cisternae along the long axis of the hair cell membrane (35). An excess of submembranous lamellae was frequent in aging outer hair cells. The functional interpretation of these findings still remains only speculative. The excess formation of lamellae might possibly be a compensatory mechanism to preserve normal contractility in aging hair cells. This interpretation is supported by the fact that an increase of such lamellae did not occur in either inner hair cells or the two types of aging vestibular hair cells, none of which (according to present knowledge) possess contractile properties. In all aging eukaryotic cells, changes in cell membranes occur in structural organization (gap junctions, cell contacts, intramembrane particles) and function (lipid microviscosity, decrease in permeability to ions) (50).

Unspecific cytoplasmic signs of cell dysfunction as, e.g., vesiculation of cytoplasm and accumulations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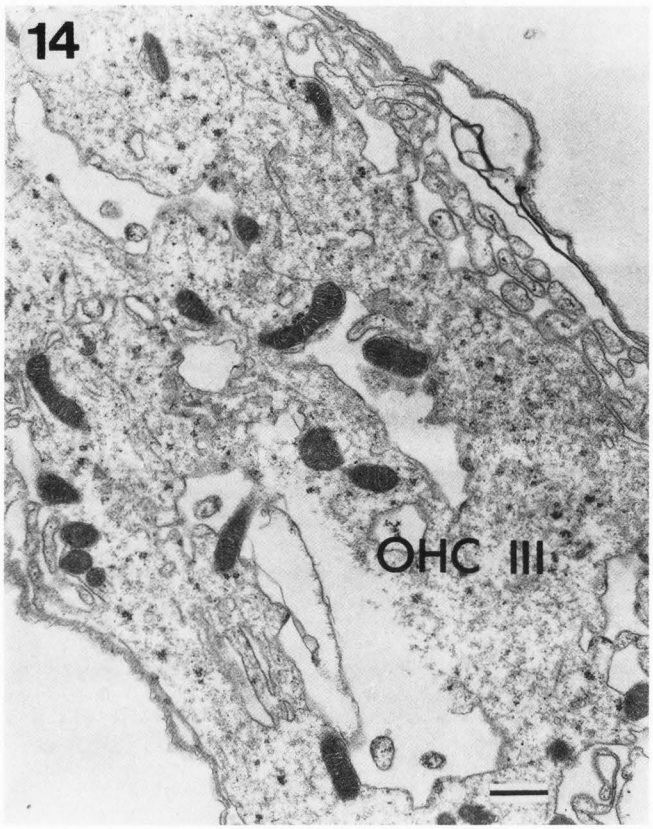
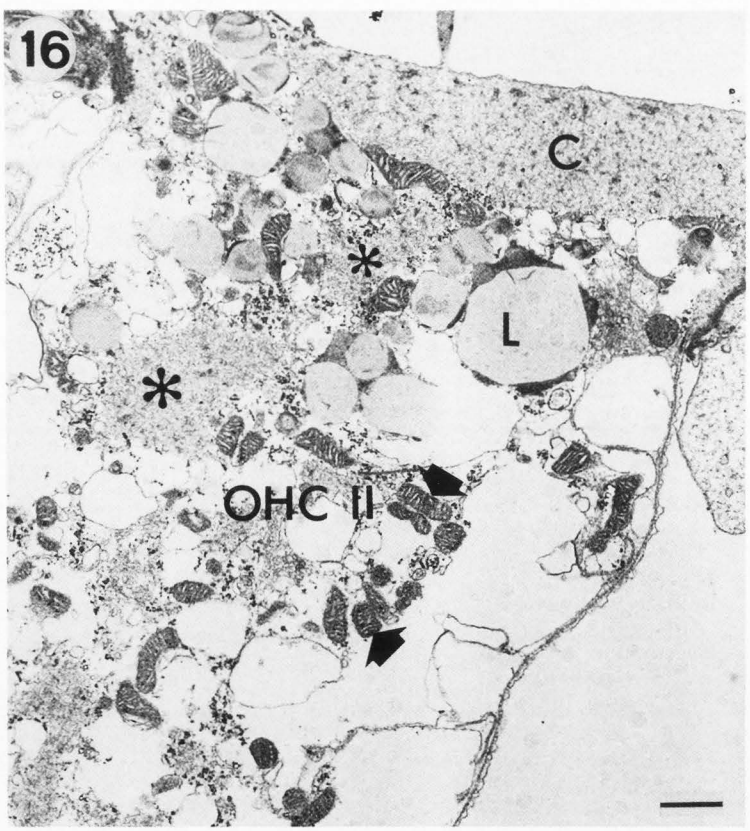

14
OHC III


15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of lipoid-like inclusions (accumulation of degenerative products) occur in all degenerating mammalian cells and are, if severe, an expression for a final common path of cell degeneration (37, 46). Lipofuscin is one of the most common signs of aging in neurons and ganglion cells in the central and peripheral nervous systems but did not occur in cochlear hair cells. In age related hair cell pathology, specific cytoplasmic changes as, e.g., disintegration of the cuticle occurred prior to unspecific changes. In hair cell pathology, primary damage to intracellular structures is uncommon. Aminoglycoside antibiotics bind initially to stereocilia and only later penetrate into the hair cell (39, 49). Noise trauma causes primary damage to stereocilia and their anchoring in the cuticular plate (19). Heavy metal poisoning primarily affects nerve endings (1). In contrast, in age related cell pathology the intracellular changes occurred primarily leaving the nerve endings and the stereocilia initially intact. In genetically induced inner ear degeneration, the disappearance of afferent contacts (synaptic bodies) in outer hair cells follows (not precedes) the loss of hair cell specializations (41) with morphologically remaining nerve endings as also found in aging vestibular hair cells (2).

Focal accumulations of intracellular electron optically dense particles in otherwise normal cytoplasm has previously been described only in vestibular hair cells following low-dose irradiation (27). The functional interpretation remains to be determined. It seems likely that these particles represent a sign of degeneration, e.g., an altered (at least initially) non-lethal change of cell metabolism.

The ultrastructural pathology in aging cochlear hair cells, mainly outer hair cells, is specific. The degeneration early affects the cuticular plate which must cause functional distortions in the perception of stimuli. This part of the age related morphological degeneration must be considered as a dysdifferentiation. Age dependent changes in cell morphology,in particular alterations of membranes, are qualitative characteristics which have an important role in determining the differentiated state of the cell. While the ultrastructural changes reflect age induced degeneration, very little is known about underlying mechanisms. The environmental influences still remain to be determined and separated from genetically determined age dependent influences on the inner ear.

Acknowledgements

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Discussion with Reviewers

RV Harrison: The old guinea pig shows hair cell and neural lesions primarily at the apex of the cochlea (Covell and Rogers 1957) rather than at the base of the high frequency region. Human presbyacusis is of course associated with the high frequencies and I wonder, therefore, if the guinea pig is a valid model for human presbyacusis.

Author: The intention with this study was to analyze the morphological quality of inner and outer hair cells in those parts of the cochlea which appeared light microscopically intact. The fine structural features of remaining hair cells were of principal importance independent of level in the cochlea.

M Mulroy: Were the increased number of vesicles observed in aged hair cells evenly distributed throughout the cytoplasm or limited to the apex or base of the cell?

Author: The vesicles were first identified in the supranuclear cytoplasm and in clusters along the cell membrane. In hair cells with advanced changes vesicles occurred throughout the cytoplasm.

M Mulroy: You make the argument that age-related cytological changes are "dysdifferentiation" rather than degeneration. How do "old" hair cells compare with developing hair cells?

Author: In aging hair cells, initial cytological changes seem to occur in the highly specialized upper cell surface area, i.e., the sensory hairs and the cuticle, without degenerative changes in any other part of the hair cell. I conclude that this is a sign of dysdifferentiation in contrast to developing hair cells which show a very early formation of sensory hairs and their underlying cuticle. Loss of a highly specialized morphology but with persisting/surviving cells for a long time is known from a number of different organ systems.

M Mulroy: How do the electron dense particles shown in figures 12 and 13 compare in size and shape with glycogen particles?

Author: The electron dense particles are 3- to 4-fold larger than glycogen particles but otherwise have a similar shape.

K Jahnke : What is the normal life span of a guinea pig?

Author: It usually does not get older than 8 years.

H Rask-Andersen: What was the morphological status of the cochleae when using the surface preparation? Do the cochleae look completely normal or can lesions be found in the basal coil?
Author: A considerable hair cell loss was found in the 4th coil. At a level of approximately 15.5 mm from the round window a normal hair cell count was found in most (but not all cochleae). A scattered hair cell loss occurred in the lower half of the basal coil (range 4-17 % missing outer hair cells) but few inner hair cells were actually missing.

H Rask-Andersen: How were the radial sections selected in relation to the occurrence of areas with total absence of hair cells?
Author: There was a distance of approximately 1.5 mm or more from severely damaged areas. All radial sections were taken from areas with an intact number of hair cells according to the cytocohleogram counting.